(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 884 319 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
16.12.1998 Bulletin 1998/51

(21) Application number: **98114130.2**

(22) Date of filing: **10.03.1993**

(51) Int. Cl.[6]: **C07D 498/04**, A61K 31/535
// (C07D498/04, 265:00, 209:00)

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **12.03.1992 GB 9205428**
05.09.1992 GB 9218846
29.12.1992 GB 9227045

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
93905561.2 / 0 630 376

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Remarks:
This application was filed on 29.07.1998 as a divisional application to the application mentioned under INID code 62.

(54) [1,3]oxazino[3,2-A]indole derivative

(57) N-[(1-^{n}Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide and its pharmaceutically acceptable salts and their use as pharmaceuticals in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

EP 0 884 319 A2

Printed by Xerox (UK) Business Services
2.16.6/3.4

Description

This invention relates to a novel compound having pharmacological activity, to a process for its preparation and to its use as a pharmaceutical.

EP-A-429984 (Nisshin Flour Milling Co., Ltd.) describes indole derivatives having 5-HT_3 receptor antagonist activity.

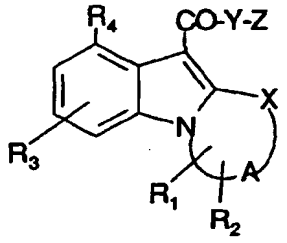
European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT_4 antagonist activity.

A novel, structurally distinct compound has now been discovered, which compound is an indole derivative 1,2-disubstituted by alkyleneoxy, with an azacyclic moiety. This compound has 5-HT_4 receptor antagonist activity.

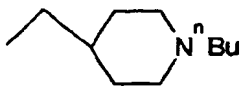
Accordingly, the present invention provides N-[(1-^{n}butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide, namely
the compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

X is O;
A is -$(CH_2)_3$- ;
R_1 R_2 R_3 and R_4 are hydrogen;
Y is NH;
Z is of formula (i):



(i)

The pharmaceutically acceptable salts of the compound of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compound of formula (I) such as the compound quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compound of the formula (I), its pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever the compound of formula (I) or a salt thereof is herein referred to.

The compound of formula (I) may be prepared by conventional coupling of the indole moiety with Z. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A and EP-A-36269 (Beecham Group p.l.c.), EP-A-429984 (Nisshin Flour Milling Co.) and EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited). It will be appreciated that the $(CH_2)_r$-O containing ring or R_3/R_4 introduction/modification may be carried out before or after coupling.

Aza(bi)cyclic side chain intermediates are known compounds or may be prepared according to the methods described in PCT/GB92/01519 and /01612 (SmithKline Beecham p.l.c.).

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

It is believed that platelet-derived 5-HT induces atrial arrhythmias which encourage atrial fibrillation and atrial disorders are associated with symptomatic cerebral and sytemic embolism. Cerebral embolism is the most common cause of ischaemic stroke and the heart the most common source of embolic material. Of particular concern is the frequency of embolism associated with atrial fibrillation.

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity may be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

The invention also provides a pharmaceutical composition comprising the compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions. Sublingual or transdermal administration is also envisaged. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colour-

ing agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of the compound of the formula (I) or a pharmaceutically acceptable salt thereof. In particular, the method comprises treatment of IBS or atrial arrhythmias and stroke.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70 kg adult will normally contain 0.05 to 1000 mg for example 0.5 to 500 mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50 mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides the compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use as a 5-HT_4 receptor antagonist in the treatment of the disorders hereinbefore described.

The invention also provides the use of the compound of formula (I) in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist in the treatment of the disorders hereinbefore described.

The following Example illustrates the preparation of the compound of formula (I); the following Description illustrates the preparation of an intermediate.

Example

N-[(1-^{n}Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide

Method 1:- A stirred solution of N-chlorosuccinimide (57 mg, 0.48 mmole) in chloroform (3 ml) was treated with a solution of N-[(1-^{n}butyl-4-piperidyl)methyl] indole-3-carboxamide (100 mg, 0.32 mmole) in chloroform (8 ml) and kept at room temperature for 2h, then treated with 3-bromo-1-propanol (0.03 ml, 0.32 mmole). After stirring for 16h, more 3-bromo-1-propanol (0.03 ml, 0.32 mmole) was added. The mixture was stirred at room temperature for a further 3h, then treated with excess 10% Na_2CO_3 solution and extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil, which was dissolved in acetone (10 ml), treated with anhydrous potassium carbonate (130 mg, 0.96 mmole) and stirred at room temperature for 16h. The mixture was concentrated *in vacuo*, the residue treated with 10% Na_2CO_3 solution (10 ml) and extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated *in vacuo* to leave a yellow oil, which was chromatographed, initially on silica gel eluting with chloroform/methanol (19:1), then on basic alumina eluting with ethyl acetate. The colourless oil obtained crystallised from ether to afford the title compound as a white solid (20 mg, 17%) mp 110-113°C.

^{1}H NMR ($CDCl_3$)

δ: 8.34 (d,1H), 7.05-7.30 (m,3H), 6.55 (t,1H), 4.53 (t,2H), 4.10 (t,2H), 3.33 (t,2H), 2.90-3.05 (m,2H), 2.25-2.45 (m,4H), 1.90-2.25 (m,2H), 1.20-1.85 (m,9H), 0.92 (t,3H).

MS (CI) MH^+ 370.

Method 2:- A stirred suspension of N-[(1-^{n}butyl-4-piperidyl)methyl] indole-3-carboxamide (120g, 0.38 mole) in chloroform (2 L) under nitrogen at room temperature was treated with freshly distilled 3-bromo-1-propanol (69 ml, 0.77 mole) followed by the portionwise addition of dry N-chlorosuccinimide (55g, 0.42 mole) over 5 minutes. The resulting yellow solution was stirred for 2.5h, then treated with 1M HCl in ether (15 ml, 0.015 mole). A moderate exotherm occurred and the reaction colour changed to orange. After a further 2h the mixture was treated with 10% Na_2CO_3 solution (700 ml) and the chloroform layer separated, dried (Na_2SO_4) and concentrated *in vacuo* to leave a thick red oil. This was treated with acetone (1.5 L) and anhydrous potassium carbonate (130g, 0.95 mole), then stirred at room temperature for 18h. The reaction mixture was concentrated *in vacuo* and the residue treated with water (1 L) and extracted with ethyl acetate (1 L). On standing a solid began crystallising from the ethyl acetate extract. After 2h at 8°C this was filtered off and dried to afford 51.7g of the title compound (E3) as a beige solid. The mother liquors were extracted with 1M HCl acid (800 ml), the acid extract then basified with K_2CO_3 and extracted with chloroform (2 x 700 ml). The combined chloroform extracts were dried (Na_2SO_4), concentrated *in vacuo* and the residue chromatographed on silica gel eluting with chloroform/methanol (96:4). A yellow oil was obtained which upon trituration with ether gave a further 21.3g of title compound as a white solid. Conversion to the hydrochloride salt and recrystallisation from ethanol/60-80 petrol gave a white solid mp 254-256°C dec.

HCl salt - ^{1}H NMR(D_2O)

δ: 7.90 (d,1H), 6.88-7.20 (m,3H), 4.35 (br t,2H), 3.70 (br t,2H), 3.40 (br d,2H), 3.20 (br d,2H), 2.9 (br t,2H), 2.65(br t,2H), 2.12 (br t,2H), 1.20-1.90 (m,9H), 0.87 (t,3H).

Elemental analysis obtained was as follows:

	Theory	Found	
Carbon	65.09	64.76,	64.75
Hydrogen	7.95	7.73,	7.77
Nitrogen	10.35	10.35,	10.36

Description (intermediate for Example)

a) **N-(1-^{n}Butyl-4-piperidyl)methylamine**

A stirred solution of isonipecotamide (70g, 0.55 mole) and 1-bromobutane (58.8 ml, 0.55 mole) in ethanol (700 ml) was treated with anhydrous potassium carbonate (152g, 1.10 mole) and heated under reflux for 3h. The mixture was allowed to cool, then filtered and the filtrate concentrated under vacuum. The residual oil was dissolved in chloroform (400 ml) and washed with water (1 x 300 ml), then dried (Na_2SO_4) and concentrated under vacuum to leave a yellow oil (77.5g). This oil was mixed thoroughly with phosphorus pentoxide (75g) and the mixture heated at 160-180°C under nitrogen for 2.5h with gentle stirring. The reaction mixture was allowed to cool, then treated with water (500 ml). When the solid mass had dissolved, the solution was basified by addition of solid K_2CO_3 and extracted with ethyl acetate (2x400 ml). The combined extracts were dried (Na_2SO_4) and concentrated *in vacuo* to leave a brown oil (78g). This was dissolved in dry ether (400 ml) and added dropwise over 30 minutes to a stirred suspension of lithium aluminium hydride (25g, 0.66 mole) in ether (200ml) at 0°C under nitrogen. When addition was complete, the mixture was allowed to warm upto room temperature and stir for 18h. It was re-cooled to 0°C and treated cautiously with water (25ml), 10% NaOH solution (25 ml) and water again (75ml). The mixture was filtered through kieselguhr and the filtrate concentrated *in vacuo* to leave a brown oil, which was distilled under vacuum to afford the title compound as a colourless oil (66g, 71%) bp 96-99°C at 3 mm Hg.

^{1}H NMR ($CDCl_3$)

δ: 2.90-3.02(m,2H), 2.58(d,2H), 2.25-2.38(m,2H), 1.65-2.00(m,4H), 1.08-1.58(m,9H), 0.92(t,3H).

b) **N-[(1-^{n}Butyl-4-piperidyl)methyl] indole-3-carboxamide**

To a stirring solution of indole-3-carboxylic acid (1g) in dichloromethane (20 ml) at 0°C under nitrogen was

added oxalyl chloride (0.81 ml) and dry dimethylformamide (3 drops). After 3 hours, the solvents were evaporated under reduced pressure. A portion of the residual acid chloride (420 mg) was dissolved in dichloromethane (12 ml) and added dropwise to a solution of N-(1-^{n}butyl-4-piperidyl)methylamine (400 mg) in dichloromethane (12 ml) followed by triethylamine (0.36 ml). After stirring at ambient temperature overnight, the reaction mixture was washed with saturated $NaHCO_3$, and the organic phase was dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue recrystallised from ethyl acetate to give the title compound (467 mg, 64%).

^{1}H NMR ($CDCl_3$) 250 MHz

δ: 9.29 (br s,1H), 8.05-7.9 (m,1H), 7.81 (d,1H), 7.55-7.4 (m,1H), 7.39-7.2 (m,2H), 6.28 (br s,1H), 3.39 (t,2H), 3.0 (br d,2H), 2.45-2.25 (m,2H), 2.1-1.1 (m,11H), 0.9 (t,3H).

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

The compound was generally active in the range of concentrations of the order of pIC_{50}=7 or more.

2) Piglet Atria

The compound was tested in the piglet spontaneous beating screen (Naunyn-Schmiedeberg's Arch. Pharmacol 342, 619-622). pK_B ($-\log_{10} K_B$) value for the compound of the Example was 10.05.

3) Rat oesophagus

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

4) 5-HT-induced motility in dog gastric pouch

The compounds is tested for inhibition in the *in vivo* method described in "Stimulation of canine motility by BRL 24924, a new gastric prokinetic agent", Bermudez *et al*, J. Gastrointestinal Motility, 1990, 2(4), 281-286.

IN VIVO TESTING FOR ANXIOLYTIC ACTIVITY

Social Interaction Test in Rats

Rats (male, Sprague Dawleys, Charles River, 250-300g) are housed in groups of eight in a holding room for 5 days. They are then housed singly in a room adjacent to the experimental room for 4 days prior to the experimental day. On the experimental day rats are administered vehicle, test compound or a benzodiazepine anxiolytic, chlordiazepoxide, p.o. in pairs (n=8-16), at 15 minute intervals beginning at 10.00 a.m. 30 mins. later they are placed with a weight matched pair-mate (encountered for the first time) in the social interaction box in a separate room. The box is made of white perspex 54 cm x 37 cm x 26 cm with a transparent perspex front side and no lid. The floor is divided up into 24 squares and the box is brightly lit (115 lux). Active social interactive behaviours (grooming, sniffing, climbing over or

under, following, biting, mounting and boxing) are scored blind for the next 15 min by remote video monitoring to give total interaction scores. The number of squares crossed by each rat is also scored and summed. After the end of each test the box is carefully wiped.

The compound of the Example increased total interaction scores over the dose range 0.01 - 10 mg/kg p.o.

Claims

1. N-[(1-^{n}Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide or a pharmaceutically acceptable salt thereof.

2. N-[(1-^{n}Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole 10-carboxamide.

3. N-[(1-^{n}Butyl-4-piperidyl)methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide hydrochloride.

4. A pharmaceutical composition comprising a compound according to any of claims 1 to 3, and a pharmaceutically acceptable carrier.

5. A composition according to claim 4 in the form of a unit dose containing 0.05 to 1000 mg of a compound according to any of claims 1 to 3.

6. A composition according to claim 5 in the form of a unit dose containing 0.5 to 500mg of a compound according to any of claims 1 to 3.

7. A composition according to any of claims 4 to 6 in the form of a tablet or capsule.

8. A compound according to any of claims 1 to 3 for use as an active therapeutic substance.

9. A compound according to claim 8 for use as a 5-HT_4 receptor antagonist.

10. A compound according to claim 9 for use as a 5-HT_4 receptor antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

11. A compound according to claim 8 for use in the treatment of irritable bowel syndrome.

12. The use of a compound according to any of claims 1 to 3 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

13. The use of a compound according to any of claims 1 to 3 in the manufacture of a medicament for the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

14. The use of a compound according to any of claims 1 to 3 in the manufacture of a medicament for the treatment of irritable bowel syndrome.

15. A process for the preparation of a compound according to claim 1 which comprises reacting an appropriate indole 10-carboxylic acid derivative with an appropriate amine.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 884 319 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
10.02.1999 Bulletin 1999/06

(43) Date of publication A2:
16.12.1998 Bulletin 1998/51

(21) Application number: **98114130.2**

(22) Date of filing: **10.03.1993**

(51) Int. Cl.[6]: **C07D 498/04**, A61K 31/535
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(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **12.03.1992 GB 9205428**
05.09.1992 GB 9218846
29.12.1992 GB 9227045

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
93905561.2 / 0 630 376

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EP 0 884 319 A3

Printed by Xerox (UK) Business Services
2.16.7/3.6

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 11 4130

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,A	EP 0 429 984 A (NISSHIN FLOUR MILING) 5 June 1991 * page 2; claims 1,9 *	1,10,12	C07D498/04 A61K31/535 //(C07D498/04, 265:00,209:00)
A	GB 1 566 307 A (HOECHST) 30 April 1980 * page 6, line 54 - line 61; claims 1,16 *	1,10,13	
P,A	EP 0 485 962 A (SYNTEX) 20 May 1992 * claim 24 *	1	
D,P, A	EP 0 501 322 A (GLAXO GROUP) 2 September 1992 * claims 1,15,16 *	1,10,12	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16 December 1998	Voyiazoglou, D

CATEGORY OF CITED DOCUMENTS

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